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(21) International Application Number: PCT/US99/12785 (22) International Filing Date: 8 June 1999 (08.06.99) (30) Priority Data: 198 27 178.6 18 June 1998 (18.06.98) DE 198 42 963.0 19 September 1998 (19.09.98) DE (71) Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. [US/US]; 900 Ridgebury Road, Ridgefield, CT 06877 (US). (72) Inventors: McNAMARA, Daniel, P.; 30 Newton Terrace, Waterbury, CT 06708 (US). DeSTEFANO, George, A.; 13 Greenknoll Drive, Brookfield, CT 06804 (US). (74) Agents: RAYMOND, Robert et al.; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).		(81) Designated States: AE, AU, BG, BR, BY, CA, CN, CZ, EE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, UZ, VN, YU, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL FORMULATIONS FOR AEROSOLS WITH TWO OR MORE ACTIVE SUBSTANCES (57) Abstract <p>The present invention relates to new pharmaceutical formulations for aerosols with at least two or more active substances for administration by inhalation or by nasal route. Specifically, the invention relates to pharmaceutical preparations for propellant-driven metered dose aerosols using a fluorohydrocarbon (HFC) as propellant, which contain a combination of active substance of two or more active substances, wherein at least one active substance is present in dissolved form together with at least one other active substance in the form of suspended particles.</p>		

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Prosecution application

5 **Pharmaceutical Formulations for Aerosols with two or more
Active Substances**

The present invention relates to new pharmaceutical
formulations for aerosols with at least two or more active
10 substances for use by inhalation or by the nasal route.

State of the art

In propellant-driven metered dose inhalers (MDI) the
15 active substances can be formulated as solutions or
suspensions. The vast majority of aerosol formulations
for MDI's are prepared as suspensions, especially if the
preparation contains more than one active substance.
Formulations in the form of solutions are used only to a
20 limited extent. In these cases, the formulations normally
contain only one active substance.

As a rule, in a suspension, the chemical stability of the
active substances is noticeably higher than in a solution.
25 Additionally, in a suspension the active substance can be
more highly concentrated than in a solution, with the
result that suspension type formulation enable higher
doses to be administered.

30 A major disadvantage of suspension-formulations is the
fact that over time (e.g. during storage) the suspended
particles clump together to form bigger, more or less
stable agglomerates or form loose flakes, sediments or
floating layers, or in the worst case, particle growth,
35 which significantly impairs the pharmaceutical quality of
the product. The size of the particles formed or the

speed of particle growth are influenced by the solubility features of the liquid phase. Thus, ingress of humidity during storage or a desired increase in polarity, e.g. achieved by adding co-solvents, can have a devastating effect on the quality of the medical end product, particularly if the suspended particles have polar structure elements. The suspension can be physically stabilised by the addition of surfactants, by reducing the harmful effects of moisture and/or particle growth so that suspended particles can be held in suspension for longer.

Natural solution-type formulations are not affected by the problems of increasing particle size or de-mixing processes such as sedimentation or flocculation. However, in this case there is a serious risk of chemical degradation. A further disadvantage is the fact that the limited solubility of the ingredients can prevent administration in high doses. In the past, the chlorofluorohydrocarbons TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane) and TG 114 (dichlorotetrafluoroethane) have proved particularly suitable as solvents. The solubility of the ingredients can be increased by the addition of co-solvents. In addition, it is usually necessary to take additional measures to chemically stabilise the dissolved components.

Up till now, CFCs such as the above-mentioned TG 11, for example, have often been used as propellants. However, since CFCs have been linked with the destruction of the ozone layer, their manufacture and use are being phased out. The intention is to replace them with special fluorohydrocarbons (HFC) which are less destructive to the ozone layer but have completely different solubility features. The toxicological profile and physico-chemical properties such as the steam pressure, for example, determine which HFCs are suitable for MDIs. The most

promising representatives at present are TG 134a (1,1,2,2-tetrafluoroethane) and TG 227 (1,1,1,2,3,3,3-heptafluoropropane).

5 For inhalative treatment it may be desirable to have aerosol formulations with two or more active substances. In such cases the active substances are formulated in the necessary concentrations as solutions or suspensions, frequently giving rise to problems regarding the chemical
10 stability of the individual substances or the degree of concentration which can be attained. Major problems are encountered if one of the active substances cannot be suspended or is unstable in a suspension-type formulation of this kind or if one of the active substances is
15 chemically unstable or will not dissolve in a solution-type formulation of this kind, particularly when HFC is used as the propellant.

It is therefore one object of the present invention to
20 develop a formulation for metering aerosols having two or more active substances which overcomes the above-mentioned disadvantages.

Description of the invention

25 Surprisingly, it has been found that a plurality of active substances can be formulated as a solution and a suspension combined in one formulation.

30 The invention relates to stable aerosol formulations with fluorohydrocarbons as propellants, particularly TG 134a and/or TG 227, consisting of two or more active substances, wherein at least one active substance is formulated as a solution and at least one active substance
35 is formulated as a suspension. The pharmaceutical preparation according to the invention is used for

inhalative treatment, particularly for treating diseases of the pharynx and respiratory tract, e.g. asthmatic diseases and COPD.

5 Detailed description of the invention

In one embodiment a medicinally useful combination of two or more active substances is used, containing beclometasone, budesonide, cromoglycinic acid, fenoterol,
10 flunisolide, fluticasone, ipratropium bromide, nedocromil, orciprenaline, oxitropium bromide, reproterol, salbutamol (albuterol), salmeterol, terbutalin, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide, the esters, salts and/or
15 solvates thereof. Which of the above-mentioned active substances is formulated as a solution and which as a suspension in the preparation according to the invention depends on the particular combinations of active substance and can be determined relatively quickly by solution and
20 suspension trials.

In a preferred embodiment, one or more of the following active substances are suspended: budesonide, cromoglycinic acid, nedocromil, reproterol and/or salbutamol (albuterol)
25 or the esters, salts and/or solvates derived from these compounds and one or more of the following substances are dissolved: beclomethasone, fenoterol, ipratropium bromide, orciprenaline and/or oxitropium bromide, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide or the esters,
30 salts and/or solvates derived from these compounds. Embodiments having two different active substances are preferred.

35 A particularly preferred embodiment contains dissolved ipratropium bromide, particularly combined with salbutamol

sulphate (albuterol sulphate) as the suspended active substance.

In all the embodiments, the active substances are used in a therapeutically effective quantity, i.e. in a quantity that can induce a successful treatment. The concentration of the active substances and the volume per stroke of spray are adjusted in such a way that the quantity of active substance which is medically necessary or recommended is released by a single spray or by a few sprays.

One embodiment relates to formulations in which the suspended particles are stabilised by the addition of surfactant substances (surfactants) or other suspension-stabilising agents to stabilise the suspended particles against physical changes. The benefit of this is that the particle size will remain pharmaceutically acceptable even over lengthy periods, e.g. during storage. Preferred particle sizes are up to 20 μm , whilst particularly preferred particle sizes are between 5 and 15 μm , best of all not exceeding 10 μm . The advantage of these particle sizes is that the particles are small enough to penetrate deeply into the lungs but not so small as to be breathed out again with the exchanged air.

Suitable surfactants and suspension-stabilising agents include all pharmacologically acceptable substances which have a lipophilic hydrocarbon group and one or more functional hydrophilic groups, especially C_{5-20} fatty alcohols, C_{5-20} fatty acids, C_{5-20} fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethylenes, polysorbates, sorbitan esters and/or carbohydrates. C_{5-20} fatty acids, propyleneglycol diesters and/or triglycerides and/or sorbitans of the C_{5-20} fatty acids are preferred, whilst oleic acid and sorbitan mono-,

di- or trioleates are particularly preferred. Alternatively, toxicologically and pharmaceutically acceptable polymers and block-polymers can be used as suspension-stabilising agents. The surfactants used are
5 either non-fluorinated or partially fluorinated or perfluorinated, the term fluorinated referring to the exchange of hydrogen radicals bound to the carbon for fluorine radicals. The quantity of surfactant may be up to 1:1 based on the proportion by weight of the suspended
10 active substances; amounts of 0.0001:1 to 0.5:1 are preferred, whilst amounts of from 0.0001:1 to 0.25:1 are particularly preferred.

A further advantage of the above surfactants is that they
15 can also be used as valve lubricants. Therefore, one embodiment relates to formulations in which said surfactants are added as valve lubricants.

In another embodiment the solubility of at least one
20 active substance to be dissolved is increased by the addition of one or more co-solvents. This has the advantage that the active substance or substances to be dissolved can be formulated in higher concentrations. The addition of co-solvent must not exceed the critical
25 threshold of polarity of the liquid phase at which one of the disadvantages described above begins to affect the suspended particles of active substance.

Suitable co-solvents are pharmacologically acceptable
30 alcohols such as ethanol, esters or water or mixtures thereof; ethanol is preferred. The concentration of the co-solvent in relation to the total formulation may be from 0.0001 to 50 wt.-%, preferably 0.0001 to 25 wt.-%. In another embodiment a concentration of 0.0001 to
35 10 wt.-% is preferred whilst particularly preferred embodiments are those wherein just enough alcohol is added

to dissolve the active substance which has to be dissolved.

In another embodiment, other common propellants are added to the HFC propellant. These added propellants may be, beside other HFCs, saturated lower hydrocarbons such as propane, butane, isobutane or pentane provided that the mixture is pharmacologically acceptable.

10 In one embodiment, stabilisers are added to the formulation, with a beneficial effect on the pharmaceutical stability of the active substances even over lengthy periods, e.g. during storage. In the context of the invention, stabilisers denotes those substances
15 which prolong the durability and usability of the pharmaceutical preparation by preventing or delaying chemical changes in the individual ingredients, particularly the active substances, e.g. caused by subsequent reactions or degradation, or those which
20 prevent biological contamination. Stabilisers which are preferred for this purpose are those which influence the pH of the liquid phase, such as acids and/or the salts thereof, particularly suitable substances are hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid,
25 ascorbic acid, citric acid and the salts thereof. In addition, preferred bactericides, fungicides etc. are benzalkonium chloride or ethylene diamine tetraacetate. Citric acid is most preferred. The concentration of the stabilisers may be up to 1000 ppm, preferably up to
30 100 ppm and most preferably 20 to 40 ppm.

One particularly preferred embodiment comprises suspended salbutamol sulphate (albuterol sulphate), dissolved ipratropium bromide, ethanol as co-solvent and citric acid
35 as stabiliser.

ExamplesExample 1

5 In a solution of liquefied 89.96 g (1 mol, 89.71 wt.-%) of
TG 134a and 10.03 g (218 mmol, 10.00% by weight) of
ethanol are dissolved 37 mg (0.09 mmol, 0.037 wt.-%) of
ipratropium bromide and 4 mg (20 μ mol, 0.004% by weight)
10 of citric acid and 210.5 mg (0.88 mmol, 0.21% by weight)
of salbutamol sulphate (albuterol sulphate) are suspended
together with 0.05% by weight of surfactant (e.g. 50 mg
(177 mmol) of oleic acid).

Example 2

15

Analogous to Example 1 using TG 227 as the propellant gas
instead of TG 134a.

Example 3

20

Disodium chromoglycate is suspended in liquefied P134 and
a small amount of ethanol and fenoterol hydrobromide is
dissolved therein.

25 Example 4

Analogous to Example 3 using TG 227 as propellant gas
instead of TG 134a.

Patent Claims

1. Pharmaceutical preparation for propellant driven
metered dose inhalers having a fluorohydrocarbon
5 (HFC) as propellant, which contain a combination of
two or more active substances characterised in that
at least one active substance is present in dissolved
form by the use of a co-solvent together with at
least one other active substance in the form of
10 suspended particles.
2. Pharmaceutical preparation according to claim 1,
characterised in that the combination of active
substances consists of two active substances.
- 15 3. Pharmaceutical preparation according to one of the
preceding claims, characterised in that the
propellant is TG 134a and/or TG 227.
- 20 4. Pharmaceutical preparation according claim 3,
characterised in that the co-solvent comprises one or
more pharmacologically tolerable alcohols, a
pharmacologically tolerable ester, water or a mixture
thereof.
- 25 5. Pharmaceutcal preparation according to claim 3,
characterised in that the co-solvent is ethanol.
6. Pharmaceutical preparation according to claim 3, 4 or
30 5 characterised in that the co-solvent is present in
a concentration of up to 25% by weight, based on the
quantity of liquefied propellant.
7. Pharmaceutical preparation according to claim 3, 4, 5
35 or 6, characterised in that the co-solvent is present

in a concentration of up to 10% by weight, based on the quantity of liquefied propellant.

- 5 8. Pharmaceutical preparation according to claim 1, 2, 3, 4, 5, 6 and 7, characterised in that the composition is stabilised by a stabiliser.
- 10 9. Pharmaceutical preparation according to claim 8, characterised in that the stabiliser contains one or more acids and/or salts.
- 15 10. Pharmaceutical preparation according to claim 8 or 9, characterised in that the stabiliser(s) contain(s) hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, ascorbic acid, citric acid, benzalkonium chloride and/or ethylene diamine tetraacetic and/or a salt thereof.
- 20 11. Pharmaceutical preparation according to claim 8 to 10, characterised in that the stabiliser is citric acid.
- 25 12. Pharmaceutical preparation according to one of the preceding claims 8 to 11, characterised in that the stabiliser is present in an amount of up to 100 ppm.
- 30 13. Pharmaceutical preparation according to one of the preceding claims 8 to 11, characterised in that the stabiliser is present in an amount of up to 40 ppm.
- 35 14. Pharmaceutical preparation according to one of the preceding claims 1 to 13, characterised in that the preparation contains a surfactant or suspension-stabilising agent.

15. Pharmaceutical preparation according to claim 14,
characterised in that the surfactant contains C₅₋₂₀
fatty alcohols, C₅₋₂₀ fatty acids, C₅₋₂₀ fatty acid
esters, lecithin, glycerides, propyleneglycol esters,
5 polyoxyethanes, polysorbates, sorbitan esters and/or
carbohydrates.
16. Pharmaceutical preparation according to claim 14,
characterised in that the surfactant contains C₅₋₂₀
10 fatty acids and/or the esters thereof.
17. Pharmaceutical preparation according to claim 14,
characterised in that the surfactant contains oleic
acid and/or sorbitan mono-, di- or trioleate.
15
18. Pharmaceutical preparation according to claim 14,
characterised in that the surfactant contains oleic
acid.
- 20 19. Pharmaceutical composition according to claim 14
characterised in that the surfactant or suspension-
stabilising agent comprises a toxicologically
acceptable polymer and/or block-polymer.
- 25 20. Pharmaceutical preparation according to one of the
preceding claims, characterised in that the active
substance combination contains beclomethasone,
budesonide, cromoglycinic acid, fenoterol,
flunisolide, fluticasone, ipratropium, nedocromil,
30 orciprenaline, oxitropium bromide, reproterol,
salbutamol, salmeterol (albuterol), terbutalin, N-
[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-
trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-
hydroxy-acetamide, the esters, salts and/or solvates
35 thereof.

21. Pharmaceutical preparation according to one of claims 1 to 20, characterised in that the active substance combination contains salbutamol sulphate (albuterol sulphate) and ipratropium bromide.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12785

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/12 A61K31/135 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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